Hemostatic alterations associated with supraceliac aortic cross-clamping

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Purpose: **The causative role of consumptive coagulopathy in the development of bleeding complications after supraceliac (SC) aortic cross-clamping (AXC) has been challenged by recent reports that ascribe this coagulopathy to primary fibrinolysis. This theory is made on the basis of evidence that tissue plasminogen activator (t-PA) antigen (Ag) levels increase after SC AXC. However, t-PA Ag levels reflect both active and inactive (bound to serum t-PA inhibitors) forms of serum t-PA, and elevations confirm the presence of fibrinolysis only in conjunction with an increase in t-PA activity.**
Methods: **To investigate the etiology of this coagulopathy, we submitted eight pigs to SC AXC and six pigs to infrarenal (IR) AXC for 30 minutes. Blood was drawn from the portal vein, the hepatic vein, and the carotid artery before AXC, just before unclamping, and 5, 30, and 60 minutes after unclamping. Prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen (FBG), platelets (PLT), thrombin-antithrombin complexes (TAT), t-PA Ag, t-PA activity, plasminogen activator inhibitor-1 (PAI-1), and α2-antiplasmin (AP) activities were measured. Statistical analysis was performed by using repeated measures analysis of variance and *t* tests.**
Results: **The PT did not differ between the two groups at any point. After unclamping, in the SC group there was a drop in PLT levels ($P = .005$), a decrease in FBG levels ($P < .001$), and a trend toward PTT prolongation ($P = .06$) compared with baseline. In contrast, there were no changes in PTT, PLT levels, or FBG levels in the IR group. TAT, a serum marker of thrombin generation, increased with SC AXC ($P = .04$), remained elevated 5 minutes after unclamping ($P = .08$), and returned to normal 30 minutes after unclamping. In contrast, TAT levels did not change in the IR control group. In the SC AXC group, the TAT levels did not differ between the three test sites at any time. SC AXC was associated with an increase in t-PA Ag just before unclamping ($P < .001$) and 5 minutes after unclamping ($P = .002$), but IR AXC was not. t-PA activity levels decreased in both experimental groups 30 and 60 minutes after unclamping. Levels of α2-AP activity decreased to a similar degree in both groups after unclamping when compared with baseline.**
Conclusion: **Thirty minutes of SC AXC results in intravascular thrombosis that cannot be localized to the ischemic visceral circulation. This intravascular thrombosis is associated with consumption of clotting factors. Thirty minutes of SC AXC causes an activation of fibrinolytic pathways that does not result in a hyperfibrinolytic state. An increase in t-PA Ag without a rise in t-PA activity does not represent true fibrinolysis, but rather an increase in the bound, inactive forms of serum t-PA. Both IR and SC AXC result in decreased fibrinolytic activity ("fibrinolytic shutdown") after release of the aortic clamp. (J Vasc Surg 2002;35:100-8.)**

Aortic cross-clamping (AXC) proximal to the celiac trunk is used during operations on the thoracoabdominal aorta for both aneurysmal and occlusive disease and less frequently during surgery for trauma and resuscitation. Major complications after supraceliac (SC) AXC result from vital organ ischemia, including the spinal cord with paraparesis/paraplegia, the kidneys with renal insufficiency/failure, and the viscera with liver failure, ischemic enterocolitis, or the development of coagulopathy.[1] Earlier reports have documented that 12% to 38% of early deaths after thoracoabdominal aneurysm repair are the direct result of bleeding complications.[2,3] In addition, 5% to 8% of patients require reoperation for bleeding in the early postoperative period, a complication which greatly increases the risk of perioperative mortality.[2-4] Such bleeding usually results from a diffuse coagulopathy unassociated with distinct identifiable sites of surgical bleeding.

The etiology of this coagulopathy is controversial. In the late 1980s, Cohen and colleagues demonstrated the presence of disseminated intravascular coagulation (DIC) after 60 and 90 minutes of SC AXC in a canine model.[5] Shunting blood to the superior mesenteric artery during clamping prevented these changes, suggesting a major causative role for gut ischemia.[6] The diagnosis of DIC in these experiments was based on prolongation of the prothrombin time (PT) and partial thromboplastin time (PTT) and a decrease in platelet (PLT) and serum fibrinogen (FBG) levels after SC AXC. These early studies have been criticized because of the lack of specificity of the coagulation studies used as a means of diagnosing DIC; more direct biochemical markers of thrombosis and fibri-

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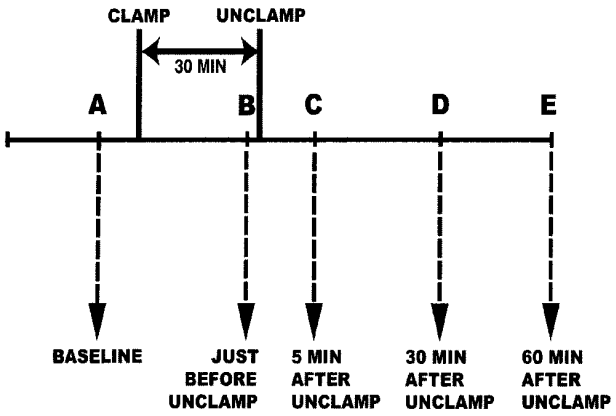

Fig 1. Time points for blood sampling.

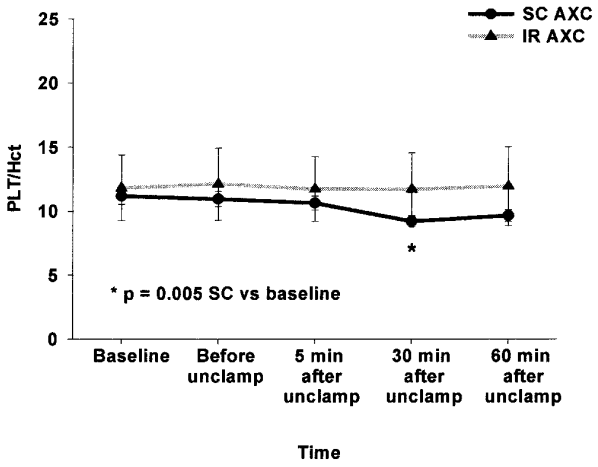

Fig 2. Platelet (*PLT*) count in the supraceliac (*SC*) and infrarenal (*IR*) aortic cross-clamping (*AXC*) groups. PLT count was corrected for dilution with the hematocrit (*Hct*).

nolysis were not available at that time. More recently, Illig and associates ascribed the development of bleeding complications with SC AXC to the induction of a primary fibrinolytic state. According to this theory, fibrinolysis results from increased production of tissue plasminogen activator (t-PA) in the ischemic mesenteric circulation and reduced t-PA clearance by the nonperfused liver.[7] The diagnosis of fibrinolysis in Illig's study, however, was made on the basis of the presence of elevated t-PA antigen (Ag) levels; t-PA activity was not measured. Recent data have proven that elevated t-PA Ag levels alone can be misleading in determining the presence of a fibrinolytic state, because Ag levels reflect both the active (free) and the inactive (bound to serum inhibitors like plasminogen activator inhibitor-1 [PAI-1]) forms of serum t-PA.[8,9]

To further investigate the etiology of this coagulopathy, we studied the hemostatic changes associated with both SC and infrarenal (IR) AXC. A porcine model was chosen for study, because of the known similarities of this species' coagulation physiology to that of humans.[10,11]

METHODS

Protocol. Market pigs weighing between 25 and 35 kg were tested for von Willenbrand disease before selection for the study. After sedation and induction of general endotracheal anesthesia with 1% to 2% isofluorane, a right neck cutdown was performed for the placement of monitoring and sampling catheters. A 7F pulmonary artery catheter was advanced through the external jugular vein to ensure optimal hemodynamic monitoring and guide fluid resuscitation during the experiment. An arterial line was placed in the carotid artery, and with fluoroscopic guidance, a 5F catheter was advanced through the external jugular vein into a hepatic vein. A rectal probe was used to monitor the animal's temperature, and normothermia was maintained throughout the experimental protocol with a heating blanket. Maintenance intravenous fluids consisted of Lactated Ringers solution at a rate of 5 to 10 mL/kg/h, with boluses as necessary to ensure hemodynamic stability. The hematocrit level was measured throughout the experiment to monitor fluid-induced hemodilution.

Through a midline abdominal incision, the aorta was dissected and controlled above the celiac trunk, just below the renal arteries and just above the aortic trifurcation. A 5F single lumen catheter was secured in the portal vein through a pancreatic venous tributary. Eight animals underwent aortic clamping above the celiac trunk and just above the aortic trifurcation (SC group), and six animals underwent aortic clamping just below the renal arteries and above the trifurcation (IR group). Both groups underwent clamping for 30 minutes, followed by unclamping and observation for 1 hour. This clamp-time was chosen because it approaches the SC clamp-time reported in clinical series in the literature.[1,7] No heparin was given before cross-clamping. Blood samples were obtained from the portal vein, the hepatic vein, and the arterial line before application of the clamps, before release of the clamps, and 5, 30, and 60 minutes after the release of the clamps (Fig 1). After the withdrawal of the last blood specimen, the animals were killed according to institutional protocol. An autopsy was performed to verify the correct placement of the hepatic vein catheter.

The study was approved by the Henry Ford Hospital Care of Experimental Animals Committee and conformed to the "Guide for the Care and Use of Laboratory Animals."

Blood tests. Blood samples were collected in tubes containing 0.5 mL of 0.5 mol/L citrate buffer, pH 4.3 (Stabilyte, Biopool International, Ventura, Calif), 0.5 mL of 0.11 mol/L sodium citrate (BD Vacutainer, Franklin Lakes, NJ), and 15% (K3) ethylenediamine tetraacetic acid (BD Vacutainer). Samples were transported immediately after collection (at room temperature) to the laboratory for processing. Plasma was isolated within 30 to 60 minutes by means of centrifugation at 1500 *g* for 15 minutes,

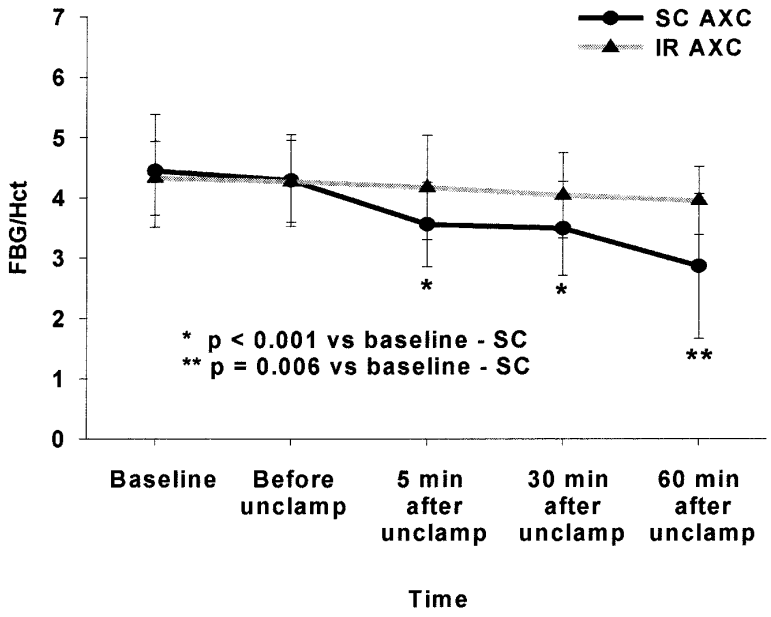

Fig 3. Fibrinogen (*FBG*) levels in the supraceliac (*SC*) and infrarenal (*IR*) aortic cross-clamping (*AXC*) groups. FBG was corrected for dilution with the hematocrit (*Hct*).

aliquoted, and frozen at –30°C. Before freezing the citrated aliquots for the specialized assays, the samples were screened for basic coagulation tests including PT, PTT, and FBG. PLT count and hematocrit level were determined by using the Coulter AcT8 (Coulter Corporation, Miami, Fla). The sodium citrated samples were used to measure thrombin-antithrombin complexes (TAT) by using the Enzygnost TAT micro, enzyme immunoassay (Dade Behring, Marburg, Germany). An enzyme-linked immunosorbent assay (TintElize t-PA, Cat# 1105, Biopool International) was used for quantitative determination of t-PA Ag. Assessment of t-PA and plasminogen activator inhibitor-1 (PAI-1) activities was accomplished by using a chromogenic assay (Spectrolyze/ fibrin, Cat# 101101, Biopool International). Activity of α2-antiplasmin (α2-AP) was measured by using the STA-Stachrom Antiplasmin chromogenic assay (Cat# 00659, Diagnostica Stago, Asnieres-Sur-Seine, France).

Statistical analysis. Results are expressed as the mean plus or minus the SEM. Analysis of variance (ANOVA) with repeated measures was used as a means of analyzing the experimental group and time effects for each parameter. First, the simultaneous effect of clamp site (group) and time was tested. If this simultaneous interaction was not significant, then the effects of clamp site (group) and time on the individual parameter were studied separately. When significant group or time or both interactions were observed ($P < .05$), Student *t* tests were used as a means of comparing the two groups at each point. Paired *t* testing was used as a means of comparing values from each point to baseline, within each experimental group. Hochberg's method was used as a means of adjusting the α level for multiple comparisons.

RESULTS

Values presented are systemic (arterial samples), unless otherwise indicated.

Hematocrit. There was a decrease in the hematocrit value after the release of the aortic cross-clamp in both experimental groups ($P < .001$ for both). There was no significant difference in the hematocrit values between the two groups at any time.

Basic tests of coagulation function. In both experimental groups, there was a significant prolongation of the PT from baseline after unclamping ($P < .001$); however, there was no difference in the PT between the two groups at any point. Although significant group ($P = .013$) and time ($P = .015$) effects on the PTT were revealed by means of ANOVA, the only significant difference detected by means of *t* tests was a longer PTT in the SC group (20.4 ± 1.1) compared with that in the IR control group (16.2 ± 0.2) 30 minutes after unclamping ($P = .006$).

There was a significant group/time effect on PLT with ANOVA ($P = .022$). In the SC group, the serum PLT count decreased from baseline 30 minutes after unclamping ($P = .005$), in contrast with that in the IR control group (Fig 2). Similarly, serum FBG levels showed a significant time/group effect with ANOVA ($P = .001$). In the SC group, the serum FBG levels decreased from baseline 5 ($P < .001$), 30 ($P < .001$), and 60 minutes ($P = .006$) after unclamping. IR FBG levels did not differ from baseline throughout the course of the experiment (Fig 3).

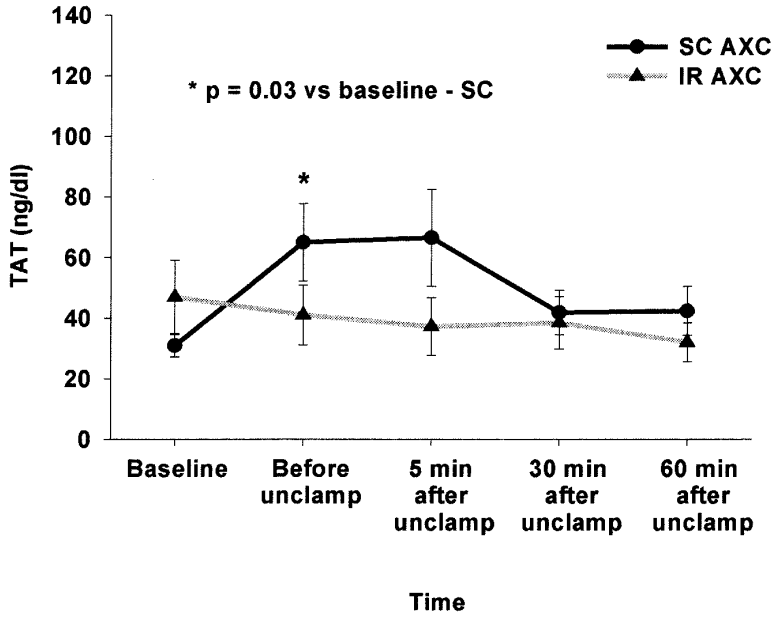

Fig 4. Thrombin-antithrombin complexes (*TAT*) in the supraceliac (*SC*) and infrarenal (*IR*) aortic cross-clamping (*AXC*) groups.

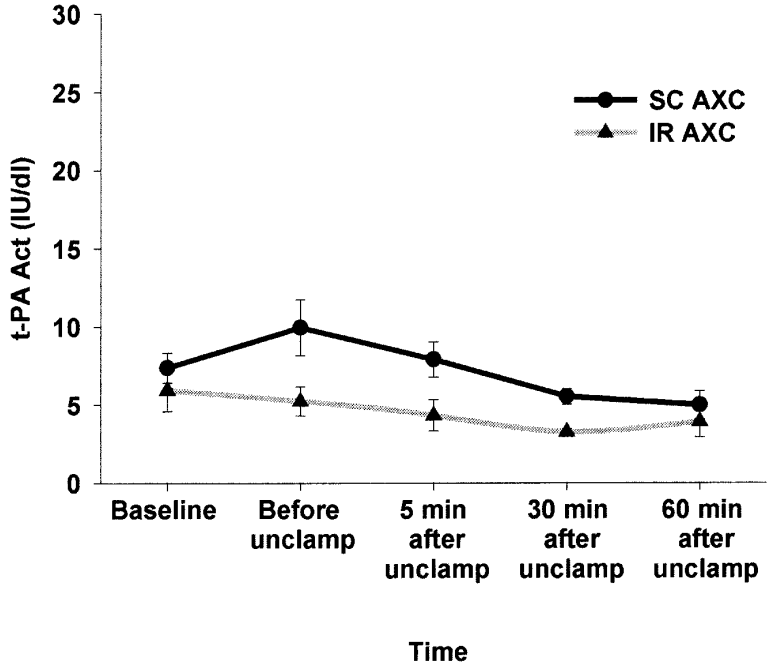

Fig 5. Tissue plasminogen activator (*t-PA*) activity (*Act*) in the supraceliac (*SC*) and infrarenal (*IR*) aortic cross-clamping (*AXC*) groups.

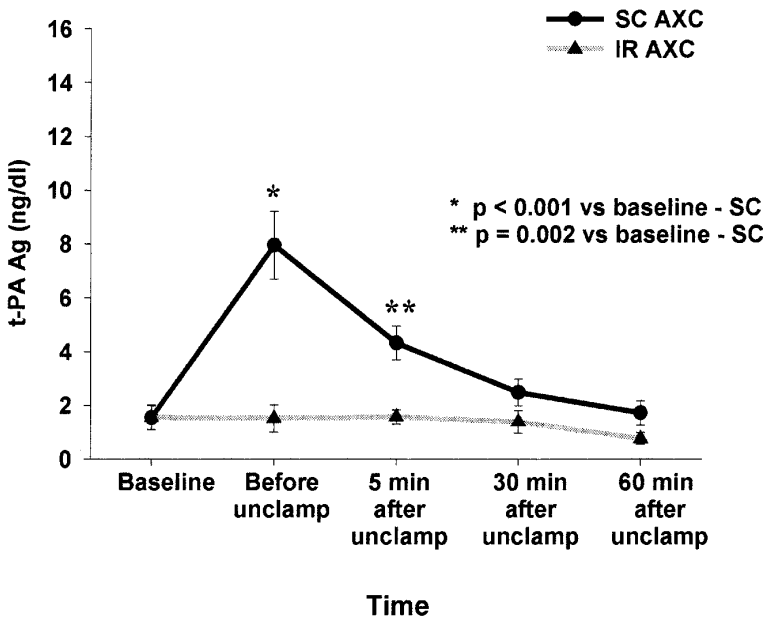

Fig 6. Tissue plasminogen activator (*t-PA*) antigen (*Ag*) in the supraceliac (*SC*) and infrarenal (*IR*) aortic cross-clamping (*AXC*) groups.

PLT and FBG values were corrected for dilution by using the hematocrit value.

Markers of thrombosis. There was a significant group/time interaction in TAT levels in the course of the experiment (ANOVA, $P = .009$). TAT levels increased from baseline in the SC group during the period of clamping ($P = .03$), but this difference was considered to be marginal when adjusting the α level for multiple comparisons (Fig 4). The TAT levels did not change in the IR control group. There was no difference in TAT levels in the SC animals between the three sampling sites (portal vein, hepatic vein, carotid artery) at any time.

Markers of fibrinolysis. The effect of group/time on t-PA activity was not significant with ANOVA ($P = .294$). t-PA activity decreased significantly with time in both groups (ANOVA, $P = .002$). In the SC group, t-PA activity levels were lower 30 ($P = .03$) and 60 minutes ($P = .04$) after unclamping, when compared with baseline; these differences were marginal, however, when adjusting the α level for multiple comparisons. In the IR group, t-PA activity was significantly lower than baseline 60 minutes after unclamping ($P = .007$; Fig 5). t-PA activity was higher in the SC group than the IR control group 30 minutes after unclamping ($P = .002$), but both values were lower than baseline at this point. There was a significant group/time effect on t-PA Ag (ANOVA, $P < .001$). SC clamping was associated with an increase in t-PA Ag levels that peaked just before unclamping, declined 5 minutes after unclamping, and returned to baseline 30 minutes after unclamping (Fig 6). At the point of maximal t-PA Ag elevation (just before unclamping), the t-PA Ag levels were higher in the portal vein (9.6 ± 1.9 ng/dL) than in the hepatic vein (6.5 ± 1.2 ng/dL; $P = .007$) or the carotid artery (8.0 ± 1.3 ng/dL; $P = .057$). IR AXC was not associated with a significant elevation in t-PA Ag levels at any time (Fig 6).

There was a significant group/time interaction in PAI-1 activity ($P = .013$). PAI-1 activity decreased progressively during the period of AXC as long as 30 minutes after release of the SC clamp, although this decrease only reached statistical significance in the hepatic vein samples and not in the portal vein or arterial samples (Figs 7 and 8). Arterial PAI-1 activity increased 60 minutes after unclamping when compared with baseline (25.0 ± 1.8 vs 18.3 ± 1.3), but this increase was marginal ($P = .04$). PAI-1 activity remained unchanged in the IR animals (Fig 8). For α2-AP activity, only time had a significant effect (ANOVA, $P < .001$). The α2-AP activity decreased similarly in both experimental groups 5, 30, and 60 minutes after release of the aortic clamps (Fig 9). The drop in α2-AP activity was not significantly different in the two groups at any time.

DISCUSSION

Thirty minutes of SC AXC caused activation of the coagulation cascade, with intense thrombin generation that subsided 30 minutes after unclamping. This activation was associated with a decrease in serum FBG levels and a drop in PLT at various intervals after unclamping. In addition, 30 minutes of SC AXC was associated with activation of fibrinolytic pathways (as evidenced by a transient rise in t-PA Ag and an initial drop in PAI-1 activity) that did not

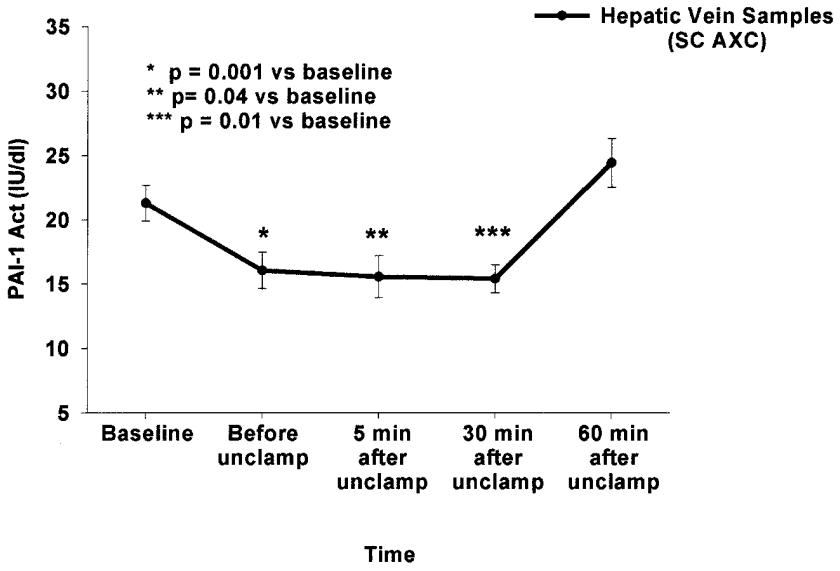

Fig 7. Hepatic vein plasminogen activator inhibitor (*PAI-1*) activity (*Act*) in the supraceliac (*SC*) aortic cross-clamping (*AXC*) groups.

result in the induction of a significant fibrinolytic state; serum t-PA activity did not increase significantly when compared with baseline values. These data strongly suggest that SC clamping results in the induction of a procoagulant state that leads to consumption of clotting factors. Is this the DIC originally suggested by Cohen?[5]

DIC is a complex reaction to tissue damage.[12-14] An insult results in widespread activation of the coagulation cascade with thrombin generation and subsequent clot formation with or without secondary fibrinolysis. Microvascular thrombosis can lead to end-organ damage. Bleeding results from clotting factor and PLT consumption (coagulopathy caused by factor depletion), when it occurs, from secondary fibrinolysis, or from a combination of factor depletion and increased fibrinolysis.[13,14] In some situations, secondary fibrinolysis is accentuated and is the predominant clinical manifestation of DIC; a classic example of this form of DIC is acute promyelocytic leukemia, in which bleeding complications caused by an increased fibrinolytic state are common, but widespread microvascular thrombosis is the predominant finding at autopsy.[14] Other types of DIC are associated with impaired fibrinolysis. Microangiopathic hemolytic anemia, for example, results in widespread activation of coagulation with down-regulation of fibrinolysis; clinical symptoms result from end-organ thrombotic complications (eg, cerebral ischemia, renal failure).[14] DIC is a confusing term because it does not accurately describe the alterations in hemostasis that are responsible for the development of coagulopathic bleeding. This project was designed as a means of separately analyzing thrombosis and fibrinolysis to systematically investigate the pathophysiology of the coagulopathy associated with SC AXC.

In pigs that were not given heparin, SC AXC clearly causes activation of the coagulation cascade. The exact mechanism that triggers this activation is unknown, but the increase in TAT levels during cross-clamping, with a return to baseline 30 minutes after unclamping, strongly implicates tissue ischemia. Adam and colleagues observed a similar prothrombotic state in patients with ruptured IR abdominal aortic aneurysms.[9] They attributed the induction of this state to whole body hypoperfusion as a result of hemorrhagic shock. Recent bench work has demonstrated that a decrease in tissue oxygen concentrations alters the local endothelial cell milieu to favor thrombosis, with monocyte activation playing a central role in this process.[15,16] The lack of significant thrombin generation during clamping in the IR control group is somewhat surprising, but may relate to a reduced ischemic tissue burden compared with SC clamping, better collateral pathways, or both.

Elevation of TAT levels to similar degrees in the three vascular beds studied is also surprising. One would expect greater increases in the ischemic tissue beds (portal vein and hepatic vein samples) than in the non-ischemic tissue beds (carotid artery samples). Two possible explanations exist. First, thrombin could indeed be generated in the ischemic tissue beds, where it is locally inactivated by antithrombin, but the TAT complexes generated are dispersed systemically. Alternatively, widespread systemic activation of coagulation even in non-ischemic tissues could be triggered by humoral factors generated during SC clamping.

The potential clinical implications of such intravascular coagulation are well recognized. Microvascular thrombosis has been associated with the development of adult

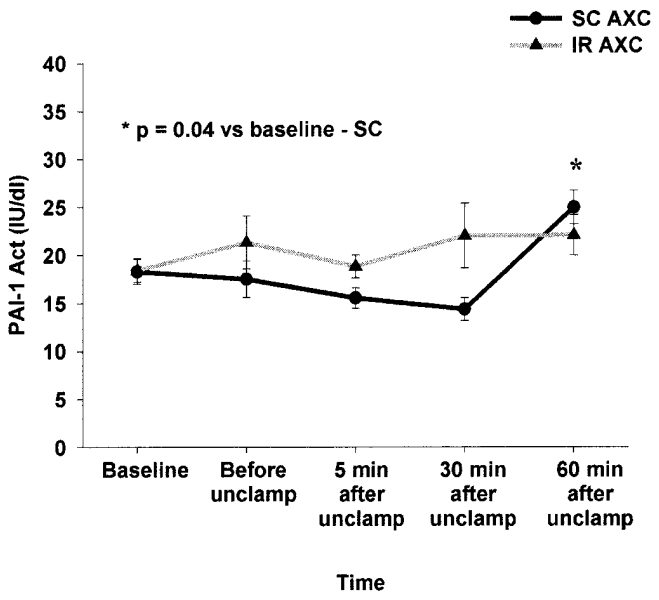

Fig 8. Plasminogen activator inhibitor (*PAI-1*) activity (*Act*) in the supraceliac (*SC*) and infrarenal (*IR*) aortic cross-clamping (*AXC*) groups.

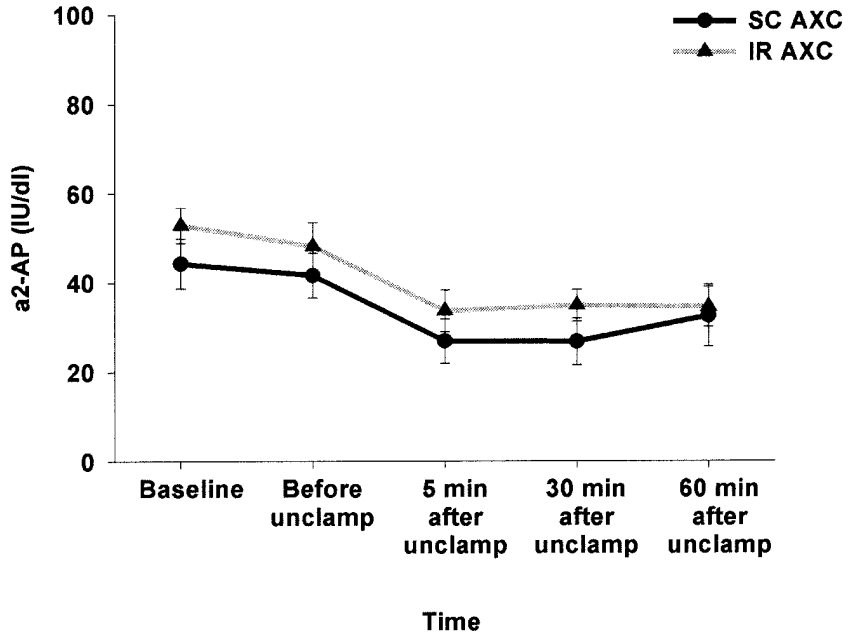

Fig 9. α 2 antiplasmin (*a2-AP*) activity in the supraceliac (*SC*) and infrarenal (*IR*) aortic cross-clamping (*AXC*) groups.

respiratory distress syndrome,[17] myocardial ischemia,[18,19] multiple organ system failure,[9,17,20,21] and death.[17,20,21] The repair of aneurysms originating above the origins of the renal and visceral arteries frequently requires SC AXC and is associated with increased morbidity and mortality rates compared with those of IR aneurysm repair. Hines and Chorost[22] reviewed their experience with SC AXC in proximal abdominal aortic aneurysm repair and reported that of the six patients who died perioperatively, one had an acute myocardial infarction and four died of multiple organ system failure. Whether widespread intravascular coagulation is in part responsible for this increased incidence of thrombotic complications after operations requiring SC clamping is unclear, but it certainly seems plausible.

In this porcine model of SC AXC, there was evidence of clotting factor consumption after unclamping. FBG levels decreased in the SC group 5 minutes after unclamping and remained low after 30 and 60 minutes. The PLT count decreased similarly after unclamping in the SC animals; this reduction was significant only at 30 minutes. Similar findings have been reported by other authors.[2,5,23] Gertler et al[2] found a significant reduction in coagulation factors 30 minutes after aortic clamping in patients undergoing thoracoabdominal aneurysm repair, compared with those in patients undergoing IR aneurysm repair. These changes subsided by the end of the operation.

The PT increased in both groups in the course of the experiment. Illig et al[7] reported similar PT prolongation in patients undergoing SC and IR AXC and attributed these changes to hemodilution. The PTT increased in the SC group 30 minutes after unclamping compared with that in the IR control group. The etiology of this PTT prolongation is not clear. If hemodilution alone was responsible for this increase, one would expect similar PTT prolongation in the IR control subjects. The PTT, however, did not change in the IR control group. This trend toward PTT prolongation may be a reflection of clotting factor consumption associated with SC AXC. Further studies are necessary to clarify this point.

Although 30 minutes of SC AXC did cause activation of fibrinolytic pathways (as evidenced by an increase in t-PA Ag with a parallel decrease in PAI-1 activity), this activation did not result in a fibrinolytic state. There was only a transient and non-significant rise in t-PA activity in this group. Furthermore, $\alpha 2$-AP activity (the main serum inhibitor of plasmin) did not differ between the SC animals and the IR control animals. If SC clamping was associated with increased fibrinolysis, one would expect a much greater drop in $\alpha 2$-AP activity than in the IR group to compensate for the increased plasmin generated. There was actually a decrease in serum fibrinolytic activity (t-PA activity) in both groups after release of the cross-clamp. A transient rise in fibrinolytic activity after ischemia with subsequent depression is a well-recognized phenomenon.[15,24,25] In addition, reduced t-PA activity and increased PAI-1 activity have been reported in the immediate postoperative period in patients undergoing infrainguinal bypass grafting procedures for severe limb ischemia.[26] This postoperative alteration in endogenous fibrinolytic activity results from an imbalance between activators and inhibitors of fibrinolysis and has been described in patients undergoing a variety of surgical procedures. This "fibrinolytic shutdown" has been implicated in the development of a number of postoperative thrombotic complications (eg, deep vein thrombosis and early arterial bypass graft occlusion).[26-29]

The results of this study conflict with the conclusions of Illig et al,[7] who ascribed the coagulopathy of SC AXC to the induction of primary fibrinolysis. These investigators found that a fibrinolytic state developed in patients undergoing SC AXC, as evidenced by decreased euglobulin clot lysis times, reduced $\alpha 2$-AP levels, and elevated t-PA Ag levels. We did not measure euglobulin clot lysis times in our study, because this test has been replaced in our institution with more reliable molecular markers of fibrinolysis (ie, t-PA activity, PAI-1 activity, and $\alpha 2$-AP activity). As mentioned earlier, we did not find any difference in the $\alpha 2$-AP activity between the two study groups, in contrast to Illig et al's results. The cause of this discrepancy is unclear. In our study, t-PA Ag increased substantially in the animals in the SC group after AXC and returned to baseline 30 minutes after clamp release, a result similar to that reported by Illig's group.[7] Recent work has documented that serum t-PA Ag is not an accurate marker of fibrinolytic activity because it reflects both the active and inactive forms (eg, bound to serum inhibitors) of serum t-PA.[9,30]

t-PA is removed from the blood by the liver and by reaction with serum inhibitors, primarily PAI-1 to form inactive (t-PA/PAI-1) complexes. The liver removes 70% to 90% of active t-PA during a single pass.[8,31] Plasma clearance of active t-PA is faster than the clearance of the t-PA/PAI-1 complex. In situations in which there is increased formation of t-PA/PAI-1 complex, the complex accumulates and contributes to the measured concentration of t-PA Ag. Thus, a rise in serum t-PA Ag does not necessarily equate with the presence of a fibrinolytic state.[8] It seems reasonable to assume that liver hypoperfusion caused by SC clamping does result in decreased hepatic clearance of serum t-PA, as suggested by Illig et al.[7] In this scenario, PAI-1 may well become the primary mechanism of t-PA inactivation, hence the increase in t-PA Ag and parallel decrease in PAI-1 activity observed in this study.

The dramatic rise in t-PA Ag seen after 30 minutes of SC clamping raises the possibility that a fibrinolytic state could develop with longer periods of SC aortic occlusion. Liver hypoperfusion during SC clamping results in decreased hepatic clearance of t-PA and increases the importance of t-PA inactivation by serum inhibitors (like PAI-1). Increased t-PA generation by the ischemic gut (the highest regional levels of t-PA Ag during SC AXC were found in the portal vein) could temporarily overwhelm serum inhibitory mechanisms and induce a fibrinolytic state with the potential for significant bleeding complications, as suggested by Illig et al. Future studies should address this issue.

In conclusion, our data show that 30 minutes of SC AXC results in systemic intravascular coagulation that is associated with consumption of clotting factors. Thirty minutes of SC AXC does not result in significant primary fibrinolysis. Both SC and IR AXC result in downregulation of fibrinolysis after unclamping. On the basis of this data, the generalized use of antifibrinolytic agents, as proposed by some authorities for treatment of the coagulopathy associated with SC AXC, does not seem reasonable. The use of an antifibrinolytic agent in a patient who is bleeding from factor depletion after activation of intravascular coagulation could lead to unopposed thrombosis with potentially devastating ischemic consequences. Anticoagulation with heparin may, however, decrease the amount of intravascular thrombosis, protect from the consumption of clotting factors, and thus prevent the development of bleeding complications.

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